Infectious Disease Epidemiology Section
Office of Public Health, Louisiana Dept of Health & Hospitals
800-256-2748 (24 hr number) – (504) 568-5005
www.oph.dhh.state.la.us

YELLOW FEVER

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Yellow fever is caused by a Flavivirus (the family include dengue, West Nile and Saint Louis encephalitis and Japanese encephalitis)

Epidemiology

Yellow fever is transmitted by Aedes aegypti and other mosquitoes. It is naturally occurring in Africa and South America (see maps below) but the anthroponotic (vector-borne person-to-person) transmission of the virus may occur wherever a suitable vector is present. In the southern United States where *A. aegypti*- is present epidemics of urban yellow fever occurred. Yellow fever was transmitted by *A. aegypti* mosquitoes that are infected after feeding on viremic humans and then spread the infection in subsequent feeding attempts.

Urban cycle
The urban cycle involves human hosts and Aedes aegypti vector. For over 200 years it was a major killer in USA port cities (1,000 deaths in the last major epidemic in New Orleans in 1905). Elimination efforts undertaken in the early 1900s led to complete elimination of dengue as urban epidemics in the Americas in 1934 (the last urban American cases occurred in northeeastern Brazil). This was one of the most successful eradication campaigns in public health.

Sylvatic cycle
The sylvatic cycle involves forest primates, principally monkeys and forest canopy mosquitoes. Human infections occur when humans get into the forest.

In the Americas the canopy mosquitoes responsible for transmission are mostly Haemagogus spp. The vast majority of human cases are male >15 years old with occupational exposure in the forest. The number of cases vary from year to year (up to 500 cases /year).

In West Africa massive immunization programs against yellow fever carried out from 1945 to 1960 had led to the disappearance of epidemic yellow fever. In the early 1960s this approach was abandoned for outbreak control measures.

Due to the sylvatic cycle, worldwide eradication is not possible. In some environments a vector-primate cycle is possible, in some other places the presence of virus is maintained by transovarial transmission in mosquitoes.

During interepidemic periods, the incidence of overt disease is below the threshold of detection by existing surveillance. Such interepidemic conditions may last years or even decades in certain countries or regions. This "epidemiologic silence" may provide a sense of false security and lead to travel without the benefit of vaccination. Surveys in rural West Africa during "silent" periods indicate that the incidence of yellow fever illness is 1.1–2.4 cases per 1,000 persons and that the incidence of death due to yellow fe-

ver is 0.2–0.5 deaths per 1,000 persons; both these ranges are less than the threshold of detection of the existing means of surveillance.

The incidence of yellow fever in South America is lower than that in Africa because virus transmission between monkeys and mosquitoes occurs in the canopy of the forest, isolated from human contact, and because immunity in the indigenous human population is high. The risks of illness and death are probably 10 times lower in South America than they are in rural West Africa, but the risks vary greatly according to specific location and season. In West Africa, the most dangerous time of year is during the late rainy and early dry seasons (July–October). Virus transmission is highest during the rainy season (January–March) in Brazil. The low incidence of yellow fever, generally a few hundred cases per year, has led to complacency among travelers. In Brazil, for example, where the majority of the population lives in coastal regions outside the endemic zone, unvaccinated recreational or vocational travelers to the interior are the usual victims of yellow fever. Four of the five cases from the United States and Europe in 1996–2002 were among travelers who were exposed in South America. All five cases were fatal. Although not as dramatic as the situation in Africa, the 1990s represented a period of increased enzootic and epizootic yellow fever transmission in South America. Brazil and Peru are currently experiencing an expansion of yellow fever virus activity, and the risk to travelers is higher than usual. The risks of illness and of death due to yellow fever in an unvaccinated traveler are estimated to be 1:1,000 and 1:5,000 per month, respectively. (For a 2-week journey, the risks of illness and death are 1:2,000 and 1:10,000, respectively.) These estimates, which are based on risk to indigenous populations, may overestimate the risk to travelers, who may have a different immunity profile, take precautions against getting bitten by mosquitoes, and have less outdoor exposure than do indigenous residents. Based on data for U.S. travelers, the risk for illness in a traveler due to yellow fever has been estimated to be 0.4–4.3 cases per million travelers to yellow fever-endemic areas.

The incubation period is 3 to 6 days.

Clinical Description

The virus replicates initially in local lymph nodes followed by blood-borne spread and further replication in liver, lung, and adrenal glands, and most prolifically in regional lymph tissue, spleen, and bone marrow. Pathologic changes are most pronounced in the liver and kidneys, but widespread hemorrhages are found on mucosal surfaces, in the skin, and within various organs. Numerous petechial hemorrhages and erosion of the gastric mucosa contribute to the hematemesis that typically introduces the illness.

It starts as a flu like illness with fever, chills, headache and backache, myalgias, nausea, vomiting, facial flushing, and conjunctival injection. In the majority of cases, resolution of this *period of infection* concludes the illness, but in others, the remission of fever for a few hours to several days is followed by renewed symptoms.

If the disease progresses, the fever remains high, the heart rate slows down (Faget's sign is high fever and bradycardia). There are headache, lumbosacral back pain, nausea, vomiting, abdominal pain, and somnolence (period of intoxication).

signs of hepatic (icterus) and renal involvement (albuminuria, leading anuria) develop. A severe hemorrhagic syndrome with gum bleeding, epistaxis, hematemesis, melena, petechiae and ecchymoses may develop. Weakness and prostration are compounded by poor intake of food and protracted vomiting. Albuminuria is a constant feature that aids in the differentiation of YF from other causes of viral hepatitis. Deepening jaundice and elevations in transaminase levels continue for several days at the same time that azotemia and progressive oliguria ensue. Direct bilirubin levels rise to 5 to 10 mg/dl, whereas alkaline phosphatase levels are only slightly raised; not infrequently, aspartate aminotransferase levels may be elevated above alanine aminotransferase levels because of myocardial damage.

Ultimately, hypotension, shock, and metabolic acidosis develop, compounded by myocardial dysfunction and arrhythmias as late events and acute tubular necrosis in some patients. Confusion, seizures, and coma distinguish the late stages of illness, but CSF examination discloses an elevated protein level without pleocytosis, consistent with cerebral edema or encephalopathy. Death usually occurs within 7 to 10 days after onset. If the patient survives the critical period of illness, secondary bacterial infections resulting in pneumonia or sepsis are frequent complications. Recovery has not been followed by chronic hepatitis.

There are no characteristic clinical signs and symptoms. Other diseases may present with a similar clinical picture: HBV infection, leptospirosis,, other hemorrhagic fevers, malaria. A definite diagnosis can only be made after laboratory confirmation: IgM antibodies, rise in IgG antibody titer, viral culture.

The disease is mild among native population in endemic areas (5% case fatality ratio) but is usually severe among travelers and during epidemics (50% case fatality ratio).

Surveillance

Yellow fever is a condition reportable within 24 hours of diagnosis.

Case Definition

Clinical description
A mosquito-borne viral illness characterized by acute onset and constitutional symptoms followed by a brief remission and a recurrence of fever, hepatitis, albuminuria, and symptoms and, in some instances, renal failure, shock, and generalized hemorrhages

Laboratory criteria for diagnosis
• Fourfold or greater rise in yellow fever antibody titer in a patient who has no history of recent yellow fever vaccination and cross-reactions to other flaviviruses have been excluded or
• Demonstration of yellow fever virus, antigen, or genome in tissue, blood, or other body fluid

Case classification
Probable: a clinically compatible case with supportive serology (stable elevated antibody titer to yellow fever virus [e.g., greater than or equal to 32 by complement fixation, greater than or equal to 256 by immunofluorescence assay, greater than or equal to 320 by hemagglutination inhibition, greater than or equal to 160 by neutralization, or a positive serologic result by immunoglobulin M-capture enzyme immunoassay]. Cross-reactive serologic reactions to other flaviviruses must be excluded, and the patient must not have a history of yellow fever vaccination.)
Confirmed: a clinically compatible case that is laboratory confirmed

Investigation

The purpose of the investigation is to confirm that the case is imported with a recent travel history to an endemic area and obtain vaccination history.

Risk to travelers

The risk of a traveler's acquiring yellow fever is determined by immunization status, geographic location, season, duration of exposure, occupational and recreational activities while traveling, and the rate of yellow fever virus transmission at the time. Although reported cases of human disease are the principal guide to the level of transmission, they may be absent (because of a high level of immunity in the population) or not detected as a result of poor surveillance. Only a small proportion of yellow fever cases are officially

notified, because of the occurrence of the disease in remote areas and lack of specific diagnostic facilities. Indeed, the majority of cases during outbreaks in Africa are missed despite an extraordinarily high incidence of infection and disease.

Immunization

A yellow fever vaccination certificate is the only certificate that could be required in international travel. There are 4 sets of requirements for yellow fever vaccination (see below). The detailed requirements for immunization against yellow fever are found in the CDC Health Information for Health Traveler which are updated yearly or WHO's International Travel and Health. Attempting to understand and apply the requirements for yellow fever vaccination can be difficult and time consuming. The most simple and safest approach is to recommend immunization to all travelers that will go to, come from or stop by any of the countries listed at the bottom.

1-Some countries require NO immunization for yellow fever, no matter where the traveller came from. Most Europeans countries, USA and Canada.

2-Some countries require yellow fever vaccine from ALL travelers. These countries are those with yellow fever transmission and the purpose is to protect the incoming traveler. Some of these are African: Benin, Burkina Faso, Cameroon, Central African Republic, Congo, Cote d'Ivoire, French Guiana, Gabon, Ghana, Liberia, Mali. Mauritania, Niger, Rwanda, Sao Tome, Senegal, Togo, Zaïre.

3-Most tropical countries require yellow fever vaccine from travelers coming FROM AN INFECTED AREA or FROM AN INFECTED COUNTRY. The purpose is to prevent the introduction of yellow fever. The list of infected countries is published regularly on the "Blue Sheet" sent regularly to all immunization clinics. Saudi Arabia is in this category.

4-Some tropical countries require yellow fever vaccine from travellrs coming from an INFECTED area or coming from ENDEMIC ZONE COUNTRIES. The countries which have such an extended requirement are: Bangladesh, Brazil, Brunei, Egypt, Guinea Bissau, Guyana, India, Indonesia, Iran, Jordan, Malaysia, Mauritius, Namibia, Pakistan, Singapore, South Africa, Sudan, Tanzania, Thailand, Uganda,

The list of ENDEMIC ZONE countries is the following: (This list varies according to sources).
AFRICA: Angola, Benin, Burkina Faso, Burundi, Cape Verde, Central African Republic, Chad, Congo, Côte d'Ivoire, Djibouti, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Mali, Madagascar, Mali, Mauritania, Mozambique, Niger, Nigeria, Rwanda, Sao Tome, Senegal, Sierra Leone, Somalia, Tanzania, Togo, Uganda, Zaïre and Zambia.
AMERICAS: Belize, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, French Guiana, Guatemala, Guyana, Honduras, Nicaragua, Panama, Peru, Suriname, Venezuela. .
CARIBBEAN: Trinidad & Tobago

Practically, vaccination is strongly recommended for people traveling outside the urban areas of countries in the yellow fever endemic zone, even if these countries have not officially reported the disease and do not require evidence of vaccination on entry. Practitioners should note that the actual areas of yellow fever activity far exceed the infected zones officially reported and that, in recent years, fatal cases of yellow fever have occurred in unvaccinated tourists visiting rural areas within the yellow fever endemic zone (WHO 1993).

The yellow fever vaccine is a suspension of live attenuated virus prepared from a strain grown in chick embryo.. The protection is effective for 10 years. The vaccine has very few side effects (redness in the area of injection, myalgia, low grade fever). It is not recommended for children less than 9 months, pregnant women, immunocompromised individuals and persons highly sensitive to eggs.

Vaccine complications:
Deaths following yellow fever vaccination: WHO issues reassurance about the continuing need for vaccination for travel to affected areas

Personal Protection Measures

In addition to vaccination, travelers should be advised to take precautions against exposure to mosquitoes when traveling in areas with yellow fever transmission. Staying in air-conditioned or well-screened quarters and wearing long-sleeved shirts and long pants will help to prevent mosquito bites. Insect repellents containing DEET should be used on exposed skin only. Permethrin-containing repellents should be applied to clothing. Travelers to rural areas should bring mosquito nets and aerosol insecticides or mosquito coils.

Hospital precaution and isolation: Standard precautions


Yellow Fever-Endemic Zones
In Africa, 02/06/2003
Gibraltar
Morocco
Algeria
Tunisia
Libya
Egypt
Western Sahara
Mauritania
Mali
Niger
Chad
Sudan
Eritrea
Djibouti
Ethiopia
Senegal
Guinea
Guinea Bissau
Burkina Faso
Benin
Nigeria
Cameroon
Côte d'Ivoire
Ghana
Togo
Liberia
Sierra Leone
Equatorial Guinea
Central African Republic
Gabon
Congo
Democratic Republic of the Congo
Uganda
Kenya
Somalia
Rwanda
Burundi
Tanzania
Angola
Zambia
Malawi
Mozambique
Zimbabwe
Namibia
Botswana
South Africa
Swaziland
Lesotho
Madagascar


Honduras
Guadeloupe
Martinique
Barbados
Nicaragua
Aruba
Trinidad and Tobago
Costa Rica
Panama
Venezuela
Suriname
Guyana
French Guiana
Colombia
Ecuador
Peru
Brazil
Bolivia
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